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Clinical study

Missed cerebrovascular events during prolonged sedation for COVID-19 pneumonia

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ABSTRACT

Cerebrovascular complications among critically ill patients with COVID-19 have yet to be fully characterized. In this retrospective case series from a single academic tertiary care referral center in New York City, we present 12 patients with ischemic or hemorrhagic strokes that were found on imaging after a period of prolonged sedation in the setting of COVID-19 pneumonia. This series demonstrates a pattern of cerebrovascular events clinically masked by deep sedation required for management of COVID-19 related acute respiratory distress syndrome (ARDS). Of the 12 patients included, 10 had ischemic stroke, 4 of which had hemorrhagic conversion, and 2 had primary intracerebral hemorrhage. Ten patients were on therapeutic anticoagulation prior to discovery of their stroke, and the remainder received intermediate dose anticoagulation (in a range between prophylactic and therapeutic levels). Additional studies are needed to further characterize the counterbalancing risks of ischemic and hemorrhagic stroke, as well as the optimal management of this patient population.

1. Introduction

Neurological complications of COVID-19 are not yet fully characterized, but recent reports suggest a possible increased frequency of stroke [1–7]. Patients with severe COVID-19 are often maintained under deep sedation for multiple weeks, and receive therapeutic anticoagulation to prevent thrombotic complications. We have observed a pattern of stroke diagnosis upon attempted waking from prolonged sedation. Presented here is a retrospective case series of twelve patients with COVID-19 pneumonia requiring mechanical ventilation and deep sedation, that were later found to have ischemic or hemorrhagic strokes upon weaning sedation (Fig. 1).

2. Methods

Between March 15th and April 26th, 2020, 1326 patients with COVID-19 were admitted to our institution (an academic, tertiary-care referral center in New York City). Among these, the 363 patients that required mechanical ventilation were screened for this analysis. Patients were included in this series if they had a new ischemic or hemorrhagic stroke seen on imaging obtained after prolonged sedation as part of COVID-19 pneumonia management. Most were diagnosed via computed tomography (CT) imaging; a small minority of patients also had magnetic resonance imaging (MRI). Patients were selected to receive imaging based on clinical suspicion of the treating physicians. Stroke etiology and classification of primary hemorrhage versus ischemic stroke with secondary hemorrhagic conversion were determined by collaborative review between the study senior neurologists and radiologist. SARS-CoV-2 infection was confirmed through reverse-transcriptase–polymerase-chain-reaction assays performed on nasopharyngeal swab specimens. Demographics, risk factors, clinical, and laboratory data were obtained from electronic health records. The Weill Cornell Medicine Institutional Review Board approved this study and waived the requirement for informed consent.

3. Results

We identified 12 cases of stroke, for which clinical characteristics are shown in Table 1. The median age was 66.5 years and 8 (66.7%) were men. All patients had at least one stroke risk factor prior to admission, most commonly hypertension (10 of 12 patients), hyperlipidemia (9 of 12 patients), or diabetes (9 of 12 patients). Five patients had atrial fibrillation, two of new onset.

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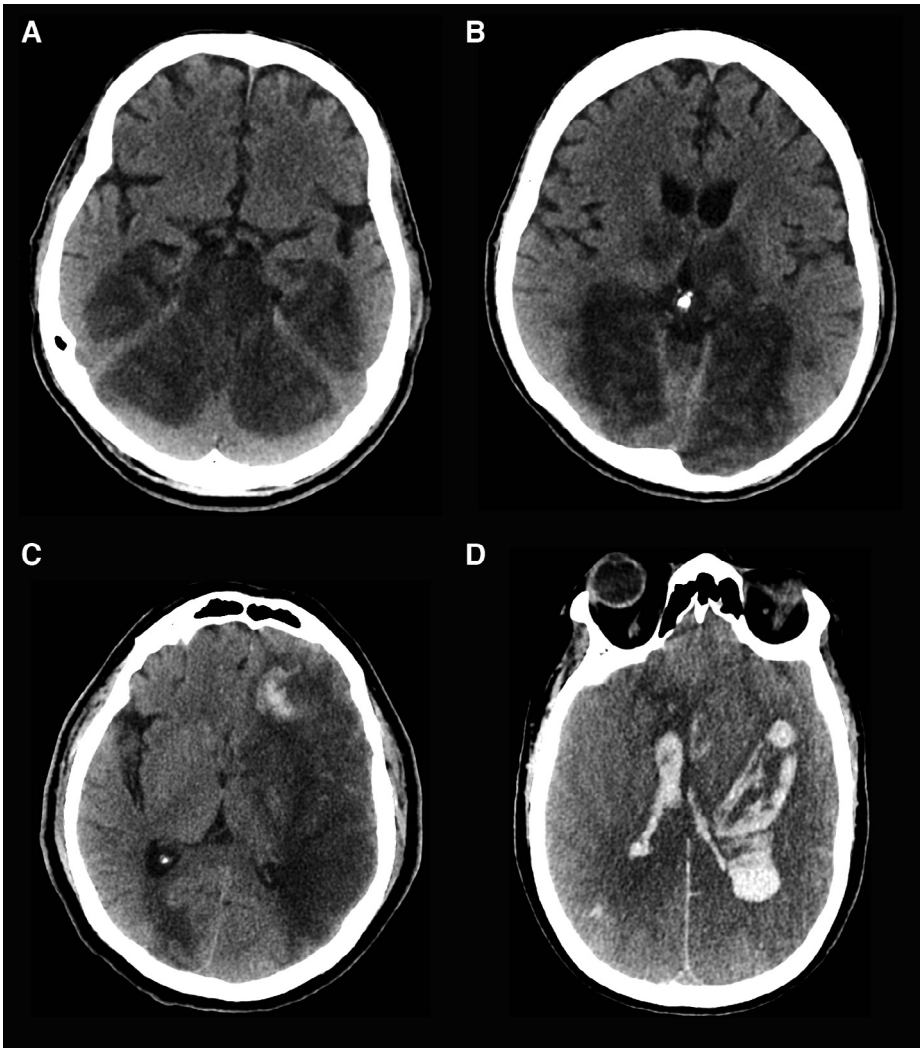

Fig. 1. A and B: Axial CT images of patient with subacute posterior circulation infarct. C: Axial CT image of subacute left middle and right parieto-occipital infarction with hemorrhagic conversion. D: Axial CT image of large left cerebral intraparenchymal hematoma with intraventricular extension.

Four patients had a history of coronary artery disease. All patients were overweight or obese based on admission body mass index. Median hospital day of intubation was day 3 (interquartile range [IQR]: 0.75–3.25), and median hospital day of stroke discovery was day 18 (IQR: 15–23.5). The median duration of mechanical ventilation prior to discovery of stroke was 16 days (IQR: 13.5–23.5). All patients had impaired consciousness, with minimal or no localizing neurological findings; pupillary abnormalities were noticeable in two patients at time of stroke discovery (anisocoria and bilateral mydriasis, respectively). All patients had raised inflammatory markers including C-reactive protein, ferritin, and IL-6. D-dimers were uniformly elevated; the median peak value was 4071 ng/mL (IQR: 2869–14,516). All twelve patients had some degree of acute kidney injury, with seven of twelve requiring renal replacement therapy. Two patients had bacteremia during their hospital course prior to stroke discovery, but had negative blood cultures at the time of imaging.

All patients had severe ARDS, with eleven requiring paralysis and six requiring prone positioning. All patients received prolonged duration of deep sedation titrated to a Richmond Agitation and Sedation Score goal of −4 to −5. Propofol was used as the primary sedative for eleven of twelve patients, while one patient used a combination of dexemedetomine and propofol. Four other patients received significant durations of additional sedating infusions such as hydromorphone, midazolam, or fentanyl to supplement propofol infusion. Eight of twelve patients received neuromuscular blockade with rocuronium infusion for a median of three days (range 1–12 days). Ten patients received therapeutic dose anticoagulation with enoxaparin, heparin infusion, argatroban, or apixaban prior to stroke discovery. Two patients received intermediate dosing (between prophylactic and therapeutic) doses of enoxaparin or heparin.

At time of writing, 6 patients were discharged from the hospital and 6 were deceased. Among patients who survived to discharge, four had full or near full recovery of mental status, while one was obtunded and one was stuporous. Two had significant residual hemiplegia.

Strokes were classified according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST criteria)[8], though logistical constraints prevented advanced vessel imaging and comprehensive cardiac evaluations in some cases. Four strokes were determined to be cardioembolic, five cryptogenic, and one large vessel disease. Among cryptogenic strokes, all would meet criteria for embolic stroke of unknown source (ESUS), as they appeared cortical and wedge-shaped. Most infarcts were determined to be subacute, as they showed significant hypodensity. Four of 10 patients with

Table 1
Clinical Characteristics of Individual Cases.

Age	Sex	Lesion	Hemorrhagic Conversion	Distribution/ Location	TOAST Classification	AnticoagulationDose	Anticoagulation Indication	Days of COVID-19 Symptoms Prior to Admission	Days of COVID-19 Symptoms Prior to Intubation	Days of COVID-19 Symptoms Prior to Stroke Discovery
74	Female	Ischemic Stroke	No	Left MCA	Cardioembolic	Therapeutic	Atrial fibrillation	7	10	22
66	Male	Ischemic Stroke	No	Left MCA, Right PCA	Cryptogenic	Therapeutic	DVT	7	7	12
67	Female	Ischemic Stroke	Yes	Bilateral Posterior Circulation	Cardioembolic	Therapeutic	Atrial fibrillation	14	19	35
63	Male	Ischemic Stroke	Yes	Left MCA	Cryptogenic	Therapeutic	CVVHD thrombosis	3	6	21
77	Male	Ischemic Stroke	Yes	Bilateral Posterior Circulation	Large Vessel Disease	Therapeutic	DVT	21	22	36
67	Female	Ischemic Stroke	No	Left MCA	Cryptogenic	Intermediate	Empiric	5	11	40
50	Female	Ischemic Stroke	No	Right Basal Ganglia	Cardioembolic	Therapeutic	Atrial fibrillation/DVT	10	10	33
66	Male	Ischemic Stroke	No	Left PCA, Right MCA	Cryptogenic	Therapeutic	Atrial fibrillation	7	9	25
77	Male	Ischemic Stroke	No	Left MCA	Cardioembolic	Intermediate	Empiric	7	11	19
60	Male	Ischemic Stroke	Yes	Left MCA, Right PCA	Cryptogenic	Therapeutic	Empiric	7	10	37
69	Male	ICH with IVH	Not applicable	Deep	Not applicable	Therapeutic	Empiric	9	10	26
58	Male	ICH with IVH	Not applicable	Lobar	Not applicable	Therapeutic	Atrial fibrillation	7	7	32

Abbreviations: MCA, middle cerebral artery; PCA, posterior cerebral artery; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; DVT, deep venous thrombosis; CVVHD, continuous veno-venous hemodialysis.

ischemic stroke had hemorrhagic conversion, confined to regions of established infarction; each had received therapeutic dose anticoagulation prior to discovery of their stroke. The median Glasgow Coma Scale at time of stroke discovery was 5 (3–7.75). Among the eight of twelve patients who had a full National Institutes of Health Stroke Scale assessed at time of imaging, median score was 21 (IQR: 15.25–28.75). For all patients, the effects of sedating medications confounded assessment of both of these scales.

Both patients with primary intracerebral hemorrhage had multicompartment hemorrhage with intraventricular extension, mass effect, midline shift, and diffuse cerebral edema, and received therapeutic anticoagulation prior to discovery of their hemorrhage. There was no clinical suspicion of hemorrhage in either case until the patients developed bilaterally dilated fixed pupils. Both patients were transitioned to comfort care and soon after died.

4. Discussion

This retrospective case series demonstrates that critically ill patients with COVID-19 not infrequently develop stroke, but due to sedation effects and a limited neurological examination, stroke diagnosis may be delayed. We present these cases to stimulate a conversation about strategies for earlier detection and optimal management.

The mechanism underlying stroke in SARS-CoV-2 infection remains unclear; direct disruption of angiotensin signaling pathways has been suggested as one possible mechanism [9]. However, infections in general are associated with increased stroke risk [10], and when combined with the known associated hypercoagulability, relatively high incidence of cardiac arrhythmia, heart failure, and myocarditis [11], and significant incidence of secondary bacteremia, patients with severe COVID-19 pneumonia have a number of systemic factors that confer high risk for stroke.

In many cases, critically ill patients with COVID-19 would not be eligible for intravenous thrombolysis and/or mechanical thrombectomy, including on the basis of unclear last known well time. Nonetheless, earlier diagnosis of stroke may be beneficial. First, it would prompt full investigation of stroke etiology, allowing clinicians to optimize secondary stroke prevention. Second, it would inform analysis of risks and benefits associated with empiric use of therapeutic and intermediate doses of anticoagulation, especially in large territory infarcts at high risk of hemorrhagic conversion. Third, it would grant important prognostic information to clinicians and patients' families, impacting decision making such as need for tracheostomy.

Our experience raises a number of questions regarding the optimal management of patients with COVID-19 ARDS. First, might regular sedation holidays be beneficial? Despite initial optimism [12], more recent evidence suggests that sedation holidays do not reduce mortality or ICU days in the larger critically ill population [13,14]. This may not be the case for COVID-19 ARDS. Second, should critically ill patients with COVID-19 infection receive surveillance CT imaging? CT is rapidly obtained, feasible in critically ill patients requiring ventilator support and close monitoring, and accurately demonstrates significant ischemia or hemorrhage. Finally, what is the utility of empiric anticoagulation in patients with COVID-19 infection? All patients included in our series received therapeutic or intermediate dose anticoagulation; 10 of 12 had ischemic strokes in spite of it, and 6 of 12 had significant hemorrhage. Guidance remains in flux regarding empiric anticoagulation in critically ill patients with COVID-19 [15]. Further studies are needed to estimate the incidence of thrombotic and hemorrhagic events and the risk-benefit profile of anticoagulation in this population.

Our results should be interpreted with caution, as this study has a number of limitations that must be considered. First, it is a small case series selected by retrospective chart review, and thus carries

a risk of bias. Second, since imaging was ordered by care teams based on clinical suspicion, not all mechanically ventilated patients routinely received brain imaging; thus, the rate of incident stroke reported in our study likely underestimates the true rate in this population of critically ill COVID-19 patients. Third, the distinction between primary hemorrhage and infarct with hemorrhagic conversion is made difficult by the presence of acute or subacute blood products that may mask underlying hypodensities, thus this distinction cannot be made with certainty given the limitations of computed tomography. Fourth, stroke etiology was determined using the TOAST classification, but this determination may be difficult when cases have clinical characteristics implying multiple possible stroke etiologies.

Much work remains to be done to accurately determine the risk of ischemic and hemorrhagic stroke in this population, and we do not present this series as fully representative of the phenomena of cerebrovascular events in COVID-19. Our experience is, however, representative of the neurology consult service at a large academic hospital during the six-week period encompassing the peak of the COVID-19 pandemic in its epicenter, New York City. We hope that this experience may impart some lessons in identifying and managing some of the most devastating complications of this deadly virus.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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